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(54) UTILISATION D'IMIDAZO(1,5-A)PYRIDO(3,2-E)PYRAZINONES
(54) USE OF IMIDAZO(1,5-A)PYRIDO(3,2-E)PYRAZINONES

(57)

The invention relates to the use of imidazo[1, 5-a]pyrido[3,2-e]pyrazinones of the formula 1 as inhibitors of phosphodiesterase 5 for the therapy of erectile dysfunction (impotence), the use of imidazo[1, 5-a]pyrido[3,2-e]pyrazinones of the formula 1 as dual inhibitors of phosphodiesterase 3 and phosphodiesterase 5 for the therapy of heart failure, of pulmonary hypertension and vessel disorders associated with hypoperfusion and process for their preparation.

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(54) **UTILISATION D'IMIDAZO(1,5-A)PYRIDO(3,2-E)PYRAZINONES**

(54) **USE OF IMIDAZO(1,5-A)PYRIDO(3,2-E)PYRAZINONES**

(57) The invention relates to the use of imidazo[1,5-a]pyrido[3,2-e]pyrazinones of the formula 1 as inhibitors of phosphodiesterase 5 for the therapy of erectile dysfunction (impotence), the use of imidazo[1,5-a]pyrido[3,2-e]pyrazinones of the formula 1 as dual inhibitors of phosphodiesterase 3 and phosphodiesterase 5 for the therapy of heart failure, of pulmonary hypertension and vessel disorders associated with hypoperfusion and process for their preparation.

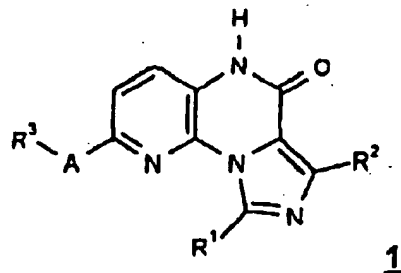
Abstract

The invention relates to the use of imidazo[1,5-a]pyrido[3,2-e]pyrazinones of the formula 1 as inhibitors of phosphodiesterase 5 for the therapy of erectile dysfunction (impotence), the use of imidazo[1,5-a]pyrido[3,2-e]pyrazinones of the formula 1 as dual inhibitors of phosphodiesterase 3 and phosphodiesterase 5 for the therapy of heart failure, of pulmonary hypertension and vessel disorders associated with hypoperfusion and process for their preparation.

USE OF IMIDAZO(1,5-A)PYRIDO(3,2-E)PYRAZINONES

Technical field

This invention relates to the use of imidazo[1,5-a]-pyrido[3,2-e]pyrazinones of the formula 1 as active ingredients for treating erectile dysfunction (impotence), process for their preparation, and to pharmaceutical preparations containing these compounds.



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This invention further relates to the use of imidazo[1,5-a]pyrido[3,2-e]pyrazinones of the formula 1 as active ingredients for treating heart failure, pulmonary hypertension and vascular disorders associated with hypoperfusion, and to pharmaceutical preparations containing these compounds.

Prior art

Male impotence can be defined as inability to engage in sexual intercourse because an erection is absent and/or ejaculation does not occur. Erectile dysfunction is the term used when the erection is insufficient in strength or duration for sexual intercourse.

About 10% of the male population suffers from erectile dysfunctions. Men between 40 and 70 years of age are particularly affected by this, about 52% being

affected. Around the world, several million men suffer from this disorder (about 7.5 million in Germany alone), which has an organic cause in most cases, and more rarely a psychological one. Erectile dysfunction is a widespread problem among elderly men, especially if other chronic disorders such as high blood pressure, atherosclerosis and diabetes are present.

Although various active ingredients are able to induce an erection, they act only after injection directly into the penis (intracavernosal, i.c.) or instillation into the urethra (intraurethral). This form of pharmacotherapy has been available for more than 10 years and comprises i.c. injection of vasoactive substances such as papaverine, phenoxybenzamine, phentolamine, moxisylyte and prostaglandin E_1 (PGE_1). However, i.c. administration of these substances is often accompanied by serious side effects such as priapism, pain or penile fibrosis. PGE_1 can be administered intraurethrally, and nitroglycerine and minoxidil can be administered transdermally (on the penis). However, this may cause side effects both in the man and in his partner.

An alternative to pharmacotherapy is surgical intervention by implantation of prostheses. This form of therapy is scarcely accepted by patients because of the later complications to be expected (infections, blood flow disturbances).

A breakthrough in the therapy of erectile dysfunction was the launch of sildenafil (Viagra®) by Pfizer in the USA and Europe. Sildenafil is an orally acting phosphodiesterase 5 (PDE5) inhibitor which does not directly cause an erection but enhances the effect of the nitric oxide (NO) released in the penis through sexual stimulation. The effect of NO, just like its second messenger cGMP, is vasodilatation in the corpus

cavernosum (erectile tissue) so that more blood can flow in, which brings about the erection.

Phosphodiesterases (PDE) are a family of isoenzymes to which it has been possible to date to assign 10 different isoenzymes. PDE enzymes cleave, by hydrolysis, cyclic guanosine 3',5'-monophosphate (cGMP) and cyclic adenosine 3',5'-monophosphate (cAMP), which occur as second messengers in a large number of cells. Phosphodiesterase 5 (PDE 5) is cGMP-specific and dominates in the tissue of the human corpus cavernosum. Inhibition of PDE 5 in the human corpus cavernosum results in an increase in the intracellular cGMP level induced by NO. This is associated with a relaxation of smooth muscles in the corpus cavernosum and consequently an erection.

PDE 5 inhibitors are thus suitable as therapeutic agents for the erectile dysfunction indication. In this connection there is a need in particular for novel PDE 5 inhibitors which can be employed as active ingredients for oral administration.

Imidazo[1,5-a]pyrido[3,2-e]pyrazinones are as yet completely unknown as active ingredients for the therapy of erectile dysfunction.

Cardiovascular disorders are one of the commonest causes of death around the world. In the WHO member states in 1998 30.9% of all deaths were attributable to cardiovascular disorders and, of these, 13.7% were attributable to coronary heart disease alone (The World Health Report 1999). Cardiovascular disorders do not, however, affect only elderly people; on the contrary, there is an increased incidence from the third decade of life onwards. They not only impair the patients' quality of life but also have great economic significance due to the direct and indirect costs. Besides genetic factors, there are contributions to the

pathogenesis of cardiovascular disorders in particular by faulty diet and obesity, alcohol and nicotine abuse, and lack of physical exercise.

Coronary heart disease is a common pathological state which comprises angina pectoris and myocardial infarct. Angina pectoris is a multifactorial pathological state caused by atherosclerosis of the coronary arteries. Flow-limiting coronary stenoses lead to myocardial hypoperfusion in the form of stable or unstable angina pectoris, silent myocardial ischaemia, ischaemic heart failure, cardiac arrhythmias or an acute myocardial infarct. The myocardial infarct is caused by the blockage of a coronary artery with a thrombus (blood clot). The thrombus usually becomes lodged at a narrowing of the coronary vessels. The regions of the myocardium lying behind this no longer receive a blood supply. The areas affected may be large or less large, depending on the site of the infarct. The basic therapy consists of eliminating the known risk factors and medical inhibition of platelet aggregation using acetylsalicylic acid or ticlopidine. The attacks of angina pectoris are treated using vasodilators such as nitrates, beta-receptor blockers or calcium channel blockers, though these may have unwanted effects such as hypotension, redistribution of blood (steal phenomenon) or cardiodepressant side effects. Patients in whom the coronary stenosis is precisely located can undergo a bypass operation (guideline: coronary heart disease/angina pectoris. Guideline 019/001 of 22 June 1998 of the Deutsche Gesellschaft für Kardiologie - Herz- und Kreislaufforschung in der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften).

Another important disorder is **heart failure**. Various factors lead to the pump output of the heart no longer being sufficient to ensure a supply of blood, and thus oxygen, to the body. Three forms of heart failure are

distinguished: right heart, left heart and global heart failure. In right heart failure, the right ventricle is no longer able to pump the required amount of blood into the pulmonary circulation. However, since blood continues to reach the right heart from the systemic circulation, because the left ventricle continues to operate uninterruptedly, the blood tails back into the abdomen, the liver and even into the legs.

Left heart failure is the term used when the left ventricle no longer provides the necessary output. In this case, the blood becomes congested in the lungs. In global heart failure, both ventricles are affected, often as the result of preceding right or left heart failure.

The treatment of cardiac insufficiency always concentrates firstly on the basic disorder, for example cardiac arrhythmias (and other cardiac disorders) or hypertension. In addition, frequently medicines to strengthen or relieve the heart (depending on the cause of the cardiac insufficiency) and dehydrating medicines (diuretics, volume reduction) are prescribed. Cardiac glycosides (for example digoxin, g-strophanthin) are often prescribed to "economize" the action of the heart, and these can be taken for a lengthy period. Inhibitors of phosphodiesterase 3 (PDE3) increase the concentration of cyclic adenosine monophosphate (cAMP) in the myocardium, increasing contractility through various cAMP-dependent protein kinases. It has been shown in various clinical studies that PDE3 inhibitors (amrinone, milrinone) are clearly positive inotropes, but continuous use tends to reduce life expectancy. The substances may therefore be employed only for treating acute stages (duration of use 2-3 weeks). This also applies to the use of β-adrenoceptor agonists such as dopamine and dobutamine, which have a direct positive inotropic effect,but are suitable only for treating an acute phase of heart failure.

The afterload is reduced by using inhibitors of angiotensin converting enzyme (ACE inhibitors, for

example captopril, enalapril) or angiotensin receptor antagonists (for example losartan), selective α1-adreno receptor blockers (for example prazosin) or organic nitrates.

A heart transplant is performed only in cases where absolutely necessary. It is the last option when all the other procedures have failed. Although transplants, including other organs, have now become routine, heart transplants are not without problems.

Pulmonary hypertension is present when the pulmonary artery pressure rises above 25 mm Hg. This leads to the development of a cor pulmonale (enlargement of the right ventricle). The causes of primary hypertension are unclear. A genetic predisposition or drug-related causes are possible. Primary pulmonary hypertension particularly affects women in the third decade of life. Secondary pulmonary hypertension is induced by impairments of the capillary circulation and may have various causes. Precapillary congestion occurs due to constriction of the pulmonary arteries in obstructive emphysema, status asthmaticus, pulmonary fibrosis or embolism. The therapy consists of reducing the pulmonary pressure and thus relieving the right ventricle. The only substances available to date are those with nonselective vasodilatory effects (ACE inhibitors, Ca channel blockers, dihydropyridines) or are used only experimentally (inhale nitric oxide (NO), epoprostenol (PGI2) or prostacycline, adenosines and PGE1, Medical and Surgical Treatment of Advanced Pulmonary Hypertension by Kenneth W. Presberg, Division of Pulmonary and Critical Care Medicine, Medical College of Wisconsin, Thoracic Medical and Surgical Management, Volume III, Number 2 1996)

Phosphodiesterases (PDE) are a family of isoenzymes to which it has been possible to assign 10 different isoenzymes to date. PDE enzymes cleave, by hydrolysis, cyclic guanosine 3',5-monophosphate (cGMP) and cyclic

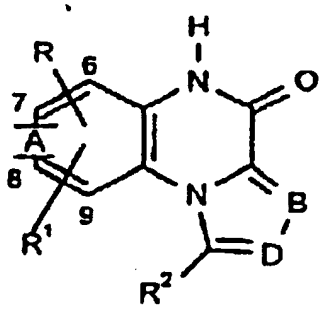
adenosine 3',5'-monophosphate (cAMP), which occur as second messengers in a large number of cells. Phosphodiesterase 3 (PDE 3) is cAMP-specific, and phosphodiesterase 5 (PDE 5) is cGMP-specific.

Of the known inhibitors of phosphodiesterases, to date only a few selective inhibitors of PDE 3 have, as already described, found limited therapeutic use for heart failure.

The invention relates to the use of imidazo[1,5-a]pyrido[3,2-e]pyrazinones of the formula 1 as active ingredients for treating heart failure, pulmonary hypertension and vascular disorders associated with hypoperfusion, which inhibits PDE 3 and PDE 5 simultaneously and comparably strongly.
The inhibition of PDE 3 in the myocardium leads in a manner known per se to an increase in contractility of the heart (positive inotropic effect). The inhibition of PDE 5 leads to vasodilatation, especially in the arterial vessels, and thus reduces, for example, the vascular resistance in the coronary vessels or the pulmonary artery.
Simultaneous utilization of the two principles of action, that is to say the positive inotropic effect on the heart combined with the releief of pressure due to dilatation of arterial vessels by one and the same active ingredient has not previously been disclosed and is technically realized for the first time by the compounds of the formula 1 according to the invention.

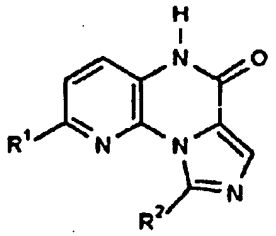
Imidazo[1,5-a]pyrido[3,2-e]pyrazinones are as yet entirely unknown as dual inhibitors of PDE 3 and PDE 5.

European Patent 0 400 583 relates to imidazo-quinoxalines of the general formula



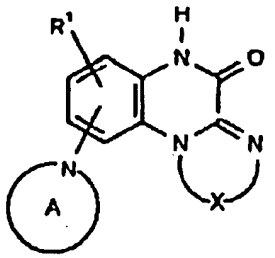
in which A denotes a nitrogen atom or CH for positions 7 or 8, B and D denote a nitrogen atom or CH, or a substituted carbon atom, and the radicals, R, R^1, R^2 represent hydrogen or various organic substituents. These compounds are stated to have a vasodilating action.

D.D. Davey et al. (J. Med. Chem. 34 (1991), 2671-2677) have described, besides various imidazo[1,2-a]-quinoxalinones, also 2 imidazo[1,5-a]pyrido[3,2-e]-pyrazinones of the formula



for which on the one hand R^1 denotes H and R^2 denotes C_2H_5,
and on the other hand R^1 denotes 2-methylimiazolo and R^2 denotes CH_3. Both compounds are characterized as PDE 3 inhibitors with a positive inotropic effect.

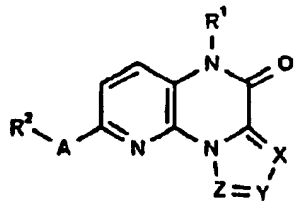
The Patent Application WO 93/20 077 relates to imidazo-quinoxalinones of the general formula



where A represents 5-membered heterocycles with 2 or 3 nitrogen atoms in the ring, R^1 can be NO_2 or CF_3, and X represents various chains having up to 4 chain members, some of which contain nitrogen.

These compounds are described as glutamate receptors antagonists with a psychotropic and antiischaemic effect.

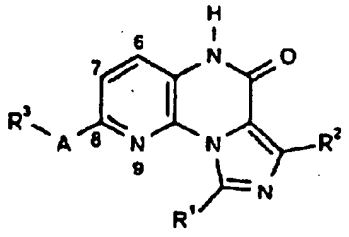
The DE Patent 195 10 965 claims pyrido[3,2-e]-pyrazinones of the formula



These also include imidazo[1,5-a]pyrido[3,2-e]-pyrazinones. However, R^1 in these is stated to be hydrogen only when A denotes N-R^3 (R^3 = H, $C_{1..6}$-alkyl). Antiasthmatic and antiallergic properties were described for the claimed group of substances.

Description of the invention

The invention relates to imidazo[1,5-a]pyrido[3,2-e]-pyrazinones of the formula 1



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in which

A represents O or NH,

R^1, R_2, R_3 can be identical or different and can denote hydrogen, and

-$C_{1..8}$-alkyl, straight-chain or branched-chain,

optionally substituted one or more times by -OH, -SH, -NH_2, -$NHC_{1..6}$-alkyl, -$N(C_{1..6}$-alkyl$)_2$,

$-NHC_{6..14}aryl$, $-N(C_{6..14}aryl)_2$, $-N(C_{1..6}alkyl)(C_{6..14}aryl)$, $-NO_2$, -CN, -COOH, $-COOC_{1..5}alkyl$, $-(C=O)C_{1..5}alkyl$, -F, -Cl, -Br, -I, $-O-C_{1..6}$-alkyl, $-O-C_{6..14}$-aryl, $-S-C_{1..6}$-alkyl-$S-C_{6..14}aryl$, $-OSO_2C_{1..6}alkyl$, $-OSO_2C_{6..14}aryl$, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles with 3..14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles with 5..15 ring members and 1..6 hetero atoms, which are preferably N, O and S,

$-C_{2..8}$-alkenyl, mono- or polyunsaturated, straight-chain or branched-chain, optionally substituted one or more times by -OH, -SH, $-NH_2$, $-NHC_{1..6}$-alkyl, $-N(C_{1..6}$-$alkyl)_2$, $-NHC_{6..14}aryl$, $-N(C_{6..14}aryl)_2$, $-N(C_{1..6}alkyl)(C_{6..14}aryl)$, $-NO_2$, -CN, -COOH, $-COOC_{1..5}alkyl$, $-(C=O)C_{1..5}alkyl$, -F, -Cl, -Br, -I, $-O-C_{1..6}$-alkyl, $-O-C_{6..14}$-aryl, $-S-C_{1..6}$-alkyl, $-S-C_{6..14}aryl$, $-OSO_2C_{1..6}alkyl$, $-OSO_2C_{6..14}aryl$, mono-, bi or tricyclic saturated or mono- or polyunsaturated carbocycles with 3..14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles with 5..15 ring members and 1..6 hetero atoms, which are preferably N, O and S,

$-C_{2..8}$-alkynyl, mono- or polyunsaturated, straight-chain or branched-chain, optionally substituted one or more times by -OH, -SH, $-NH_2$, $-NHC_{1..6}$-alkyl, $-N(C_{1..6}$-$alkyl)_2$, $-NHC_{6..14}aryl$, $-N(C_{6..14}aryl)_2$, $-N(C_{1..6}alkyl)(C_{6..14}aryl)$, $-NO_2$, -CN, -COOH, $-COOC_{1..5}alkyl$, $-(C=O)C_{1..5}alkyl$, -F, -Cl, -Br, -I, $-O-C_{1..6}$-alkyl, $-O-C_{6..14}$-aryl, $-S-C_{1..6}$-alkyl, $-S-C_{6..14}aryl$, $-OSO_2C_{1..6}alkyl$, $-OSO_2C_{6..14}aryl$, mono-, bi or tricyclic saturated or mono- or polyunsaturated carbocycles with 3..14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles with 5..15 ring members and 1..6 hetero atoms, which are preferably N, O and S,

-mono-, bi- or tricyclic, saturated or mono- or polyunsaturated carbocycles with 3..14 ring members,
optionally substituted one or more times by -OH, -SH, $-NH_2$, $-NHC_{1..6}$-alkyl, $-N(C_{1..6}\text{-alkyl})_2$, $-NHC_{6..14}$aryl, $-N(C_{6..14}\text{aryl})_2$, $-N(c_{1..6}\text{alkyl})(C_{6..14}\text{aryl})$, $-NO_2$, -CN, -COOH, $-COOC_{1..5}$alkyl, $-(C{=}O)C_{1..5}$alkyl, -F, -Cl, -Br, -I, $-O\text{-}C_{1..6}$-alkyl, $-O\text{-}C_{1..14}$-aryl, $-S\text{-}C_{1..6}$-alkyl, $-S\text{-}C_{6..14}$aryl, $-OSO_2C_{1..6}$alkyl, $-OSO_2C_{6..14}$aryl,

-mono-, bi or tricyclic saturated or mono- or polyunsaturated heterocycles with 5..15 ring members and 1..6 hetero atoms, which are preferably N, O and S,
optionally substituted one or more times by -OH, -SH, $-NH_2$, $-NHC_{1..6}$-alkyl, $-N(C_{1..6}\text{-alkyl})_2$, $-NHC_{6..14}$aryl, $-N(C_{6..14}\text{aryl})_2$, $-N(C_{1..6}\text{alkyl})(C_{6..14}\text{aryl})$, $-NO_2$, -CN, -COOH, $-COOC_{1..5}$alkyl, $-(C{=}O)C_{1..5}$alkyl, -F, -Cl, -Br, -I, $-O\text{-}C_{1..6}$-alkyl, $-O\text{-}C_{1..14}$-aryl, $-S\text{-}C_{1..6}$-alkyl, $-S\text{-}C_{6..14}$aryl, $-OSO_2C_{1..6}$alkyl, $-OSO_2C_{6..14}$aryl.

It is an essentially constituent of this invention that the compounds of formula 1 have a nitrogen atom in position 9, and that the fragment A with A = O or NH is present, as essential structural precondition for the use according to the invention as therapeutic agents for treating erectile dysfunction.

The compounds according to the invention of the formula 1 with A = O are novel. The compounds according to the invention of the formula 1 with A = NH are known per se from the Patent DE 195 10 965, to which reference has already been made in the prior art.

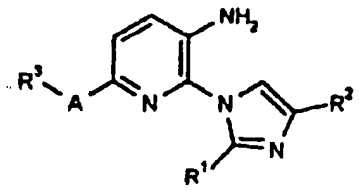
The invention also relates to the physiologically tolerated salts of the compounds of formula 1, which can be obtained by neutralizing the bases with inorganic or organic acids or by neutralizing the acids

with inorganic or organic bases, or by quaternizing tertiary amines to give quaternary ammonium salts.

In the case of compounds of formula 1 with an asymmetric carbon atom, the invention relates to the D form, the L form and D,L mixtures and, in the case of more than one asymmetric carbon atom, the diastereomeric forms.

The invention further relates to a process for preparing the compounds according to the invention of formula 1.

The compounds of the general formula 1 with the meanings of A, R^1, R^2 and R^3 described previously are prepared according to the invention by reacting 3-aminopyridines with the formula 2 with identical meanings of A, R^1, R^2 and R^3



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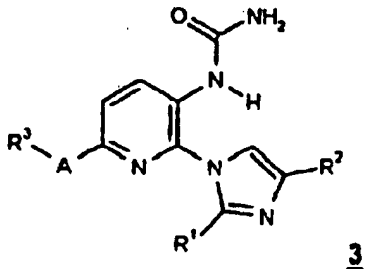
in an organic solvent in the presence of an acid with a cyanate. The ureas of the formula 3 with identical meaning of A, R^1, R^2 and R^3 which are produced in this way



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are subsequently heated in an organic solvent so that cyclization to the compounds according to the invention of the formula 1 takes place.

A variant for preparing the ureas of the formula 3 which is particularly preferred for the purpose of the preparation processes according to the invention comprises the use of alkali metal cyanates.

A variant for preparing the ureas of the formula 3 which is preferred for the purpose of the preparation processes according to the invention comprises reacting in protic solvents, particularly preferably in acetic acid.

A variant for preparing the ureas of the formula 3 which is preferred for the purpose of the preparation processes according to the invention comprises reacting in the presence of a mineral acid, particularly preferably in the presence of a concentrated mineral acid which is miscible with the solvent used, such as, for example, in the presence of concentrated hydrochloric acid.

A variant for cyclizing the ureas of the formula 3 which is preferred for the purpose of the preparation processes according to the invention to form the compounds according to the invention of the formula 1 comprises the use of solvents with a boiling point of > 80°C, particularly preferably of solvents with a boiling point of > 100°C.

A variant for cyclizing the ureas of the formula 3 which is preferred for the purpose of the preparation processes according to the invention to form the compounds according to the invention of the formula 1 comprises carrying out the reaction at a reaction temperature of > 80°C, particularly preferably at a reaction temperature of > 100°C.

A particular advantage of the compounds according to the invention is that they can be administered orally

as novel therapeutic agents for the erectile dysfunction indication.

It is a further constituent of this invention that the solution, described in the examples, of the compounds according to the invention is particularly preferably used for oral administration.

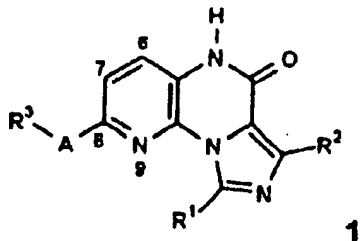
Oral administration of 5-200 mg of the compound before sexual intercourse represents the preferred therapeutic plan. The compound can also be used as solution parenterally, orally, buccally or sublingually.

Medicinal products which contain one or more of the compounds according to the invention of the formula 1 in addition to conventional physiologically tolerated carriers and/or diluents or excipients, and process for producing these medicinal products, are likewise a constituent of this invention.

The compounds according to the invention of the formula 1 and the medicinal products which contain the compounds according to the invention of the formula 1 can be employed both singly and in combination with one another.

It is a further constituent of this invention that the compounds according to the invention can be used as therapeutic agents in veterinary medicine for the prophylaxis and therapy of erectile dysfunction in male mammals. The dosage, the administration plan and pharmaceutical formulation of the compound take account of species differences and the requirements of veterinary practice.

The invention furthermore relates to those imidazo[1,5-a]pyrido[3,2-e]pyrazinones of the formula 1



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in which

A represents O or NH,

R^1 and R^2 can be identical or different and can denote hydrogen, and

$-C_{1...5}$-alkyl, straight-chain or branched-chain, optionally substituted one or more times by -OH, -SH, $-NH_2$, $-NO_2$, -CN, -COOH, -F, -Cl, -Br, -I, $-O-C_{1...6}$-alkyl, $-S-C_{1...6}$-alkyl, and

R^3 represents hydrogen, and

$-C_{1...5}$-alkyl, straight-chain or branched-chain, optionally substituted one or more times by -OH, -SH, $-NH_2$, $-NO_2$, -CN, -COOH, -F, -Cl, -Br, -I, $-O-C_{1...6}$-alkyl, $-S-C_{1...6}$-alkyl or phenyl,

their use as therapeutic agents for treating heart failure, pulmonary hypertension and vascular disorders associated with hypoperfusion.

It is an essential constituent of this invention that the compounds of formula 1, as an essential structural precondition for the use according to the invention as therapeutic agents for treating heart failure, pulmonary hypertension and vascular disorders associated with hypoperfusion, both have a nitrogen atom in position 9 and comprise a fragment A with A = O or NH.

Concerning the use of the said compounds of the formula 1 as therapeutic agents for treating heart failure, pulmonary hypertension and vascular disorders associated with hypoperfusion, the invention also relates to the physiologically tolerated salts of these compounds, which can be obtained by neutralizing the

bases with inorganic or organic acids or by neutralizing the acids with inorganic or organic bases, or by quaternizing tertiary amines to give quaternary ammonium salts.

Concerning the use of the said compounds of the formula 1 as therapeutic agents for treating heart failure, pulmonary hypertension and vascular disorders associated with hypoperfusion, the invention relates in the case of compounds with an asymmetric carbon atom to the D form, the L form and D,L mixtures and, in the case of more than one asymmetric carbon atom, the diastereomeric forms.

Concerning the use of the said compounds of the formula 1 as therapeutic agents for treating heart failure, pulmonary hypertension and vascular disorders associated with hypoperfusion, the compounds according to the invention can be administered both systemically, for example intravenously, intramuscularly and subcutaneously, and orally. Oral administration of the compounds according to the invention is particularly preferred.

A further constituent of this invention is that the solution of the compounds according to the invention which is described in the examples is particularly preferably used for oral administration for the use of the said compounds of the formula 1 as therapeutic agents for treating heart failure, pulmonary hypertension and vascular disorders associated with hypoperfusion.

The compounds can also be used parenterally, buccally or sublingually as solutions.

Pharmaceuticals containing one or more of the said compounds of the formula 1 according to the invention in addition to conventional physiologically tolerated

carriers and/or diluents or excipients, and processes for producing these pharmaceuticals, are likewise a constituent of this invention.

The said compounds of the formula 1 according to the invention and the pharmaceuticals containing the said compounds of the formula 1 according to the invention can be employed both singly and in combination with one another.

The said compounds of the formula 1 according to the invention inhibit PDE 3 and PDE 5 *in vitro* simultaneously and comparably strongly.

It has been found that the said compounds of the formula 1 according to the invention bring about *in vivo* an increase in the contractility of the heart (positive inotropic effect) and at the same time vasodilatation, especially in the arterial vessels.

It is a constituent of this invention that the described dual principle of action of the compounds according to the invention makes it possible to suppress the risks of serious changes in blood pressure and of hypoxia-related arrhythmias.

It is an aspect of this invention that the compounds of the formula 1 can be used in particular for treating the acute phase of heart failure, of coronary heart disease and of cor pulmonale.

Examples

8-Methoxy-3-methyl-1-propylimidazo[1,5-a]pyrido[3,2-e]-pyrazinone (1)

29.6 g (0.1 mol) of 3-amino-6-methoxy-2-(4-methyl-2-propyl-1-imidazolyl)pyridine are introduced into 165 ml of acetic acid, and a solution of 11.8 g (0.14 mol) of potassium cyanate in 15 ml of water is added. Then, while stirring, 15.5 ml of concentrated hydrochloric acid (37% strength) are added, and the

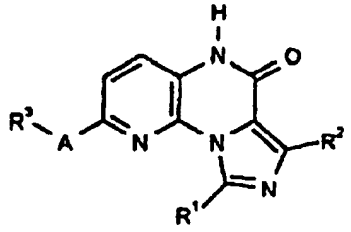
mixture is stirred at 25-30°C for 4 hours. 400 ml of water are then added to the reaction solution, and the pH is adjusted to 8 with concentrated sodium hydroxide solution. N-[6-Methoxy-2-(4-methyl-2-propyl-1-imidazolyl)-3-pyridyl]urea crystallizes out while cooling in ice. This intermediate is separated off, washed with water and dried at 60°C.

This urea is boiled under reflux in 100 ml of DMF for 4 hours. The product crystallizes out by subsequently cooling the reaction solution with ice. It is separated off, washed with DMF and dried at 80°C.

Yield: 14 g (51% of theory)

Melting point: 294-295°C

Numerous other compounds of the formula 1 can be prepared by using the variant indicated in the example, of which the following are listed by way of example:



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Comp.	A	R^1	R^2	R^3	Melting point [°C]
1	O	C_3H_7	CH_3	CH_3	294-295 (DMF)
2	O	H	H	CH_3	314-317 (DMF)
3	O	H	CH_3	CH_3	321-323 (DMF)
4	O	CH_3	H	CH_3	309-311 (DMF)
5	O	C_3H_7	H	CH_3	289-290 (DMF)
6	O	C_2H_5	CH_3	H	320 decomp. (DMF)
					314-315

Comp.	A	R^1	R^2	R^3	Melting point [°C]
7	O	C_2H_5	CH_3	CH_3	(DMF)
8	NH	C_2H_5	CH_3	CH_2-C_6H_5	276-278 (DMF)
9	O	C_2H_5	CH_3	$(CH_2)_3$-OH	303-305 decomp. (DMF)
10	O	C_2H_5	CH_3	$CH_2(C=O)CH_3$	312-314 decomp. (DMF)
11	O	C_2H_5	CH_3	CH_2-2-pyridyl	299-301 (DMF)
12	O	C_6H_5	H	CH_3	323 (DMF)
13	O	H	C_6H_5	CH_3	326 decomp. (DMF)

Preparation of a solution for oral administration of compound 1

Compound 1 can be dissolved in 1 N hydrochloric acid for example in the ratio of 10-50 mg per ml. Further dilution with distilled water to which 10% by volume of polyethylene glycol 660 12-hydroxystearate (Solutol® HS 15) are added, in the ratio of 1:9, results in a clear solution which contains 1-5 mg/ml of compound 1 and can be used as drinkable or injectable solution.

Biological effects of the compounds according to the invention with respect to their use for the therapy of erectile dysfunction.

The compounds according to the invention are strong inhibitors of phosphodiesterase 5. Their therapeutic potential is demonstrated *in vitro* for example by the enhancement of the effect of NO on the intracellular cGMP level in rat fibroblasts and the relaxation of human corpus cavernosum.

Phosphodiesterase 5 inhibition

The PDE 5 activity is determined in enzyme preparations from human platelets. Human blood was anticoagulated with citrate. Centrifugation at 700 x g for 20 minutes at room temperature allows the platelet-rich plasma in the supernatant to be separated from the erythrocytes and leucocytes. The platelets are lysed by ultrasound and employed in the PDE 5 assay.

The phosphodiesterase activity is determined by the method described by Thompson et al. (Thompson, W.J.; Appleman, M.M., Assay of cyclic nucleotide phosphodiesterase and resolution of multiple molecular forms of the enzyme. Adv. Cycl. Nucl. Res. 1979, 10, 69-92) with some modifications.

The reaction mixtures contain 50 mM tris-HCl (pH 7.4), 5 mM $MgCl_2$, the inhibitors in variable concentrations, the enzyme preparation and the other components necessary to measure the individual isoenzyme PDE 5 (see below). The reaction is started by adding the substrate, 0.5 μM [^{3}H]-cGMP (about 6000 CPM/assay). The final volume is 100 ml.

Test substances are made up as stock solutions in DMSO. The DMSO concentration in the reaction mixture is 1% v/v. This DMSO concentration has no effect on PDE 5 activity. After the reaction has been started by adding substrate, the samples are incubated at 37°C for 30 minutes. The reaction is stopped by heating the test tubes at 110°C for 2 minutes. The samples remain in ice for a further 10 minutes. Addition of 30 μl of 5'-nucleotidase (1 mg/ml, from a suspension of Crotalus adamanteus snake venom) is followed by incubation at 37°C for 10 minutes. The samples are stocked on ice, 400 μl of a Dowex-water-ethanol (1+1+1) mixture are added to each and, after thorough mixing, they are incubated on ice again for 15 minutes. The reaction vessels are centrifuged at 3000 x g for 20 minutes. 200 μl aliquots of the supernatant are transferred

directly into scintillation vessels. After addition of 3 ml of scintillator, the samples are measured in a beta counter. The nonspecific enzyme activities are measured in each case in the presence of 100 μM IBMX in the PDE 5 determination and are subtracted from the assay values.

The IC_{50} values for phosphodiesterase 5 inhibition determined for the compounds according to the invention were in the range from 10^{-9} to 10^{-5} M.

For example, the following values were determined for selected examples:

Example	IC_{50} [μmol/l]
1	0.01
5	0.12
7	0.10
8	0.07

Induction of NO production in fibroblasts (rat)

Rat fetal lung fibroblasts (RFL-6) represent a suitable medium for investigating the influence on the effect of NO on intracellular cGMP levels (Ishii et al. 1991). The basic mechanism is applicable to smooth vascular muscles in the corpus cavernosum.

The compounds according to the invention enhance, in a concentration-dependent manner, the increase in intracellular cGMP levels induced by the NO donor S-nitroso-N-acetyl-D,L-penicillamine.

Thus, compound 1 at a concentration of 0.010 μmol/l for example induces a significant rise in the cGMP level. The activity of compound 1 is thus 10,000 times that achieved by use of the nonspecific PDE inhibitor 3-isobutyl-1-methylxanthine (IBMX).

Relaxation of human corpus cavernosum *in vitro*

Strips of human corpus cavernosum in an organ bath are precontracted with noradrenaline. The relaxant effect of test compounds is measured as a function of the concentration.

The compounds according to the invention have a relaxant effect, depending on the concentration, on the corpus cavernosum strips precontracted with noradrenaline. Thus, for example, an EC_{50} of 0.35 µmol/l was measured for compound 1.

Biological effects of the compounds according to the invention with respect to their use for the therapy of heart failure, of pulmonary hypertension and vascular disorders associated with hypoperfusion

The said compounds of the formula 1 according to the invention are dual inhibitors of phosphodiesterase 3 and phosphodiesterase 5. Their therapeutic potential is demonstrated *in vitro* for example by the enhancement of the effect of NO on the intracellular cGMP levels in rat fibroblasts.

Inhibition of phosphodiesterase 3

The PDE 3 activity is determined in enzyme preparations from human platelets. Human blood was anticoagulated with citrate. Centrifugation at 700 x g for 20 minutes at room temperature allows platelet-rich plasma in the supernatant to be separated from the erythrocytes and leukocytes. The platelets are lysed by ultrasound and employed in the PDE 3 assay. The phosphodiesterase activity is determined by the method described by Thompson et al. (Thompson, W.J.; Appleman, M.M., Assay of cyclic nucleotide phosphodiesterase and resolution of multiple molecular forms of the enzyme. Adv. Cycl. Nucl. Res. 1979, 10, 69-92) with some modifications.

The reaction mixtures contain 50 mM tris-HCl (pH 7.4),

5 mM $MgCl_2$, the inhibitors in variable concentrations, the enzyme preparation and the other components necessary to measure the individual isoenzyme PDE 3 (see below). The reaction is started by adding the substrate 0.5 µm [^{3}H]-cAMP (about 6000 CPM/assay). The final volume is 100 ml.

Test substances are made up as stock solutions in DMSO. The DMSO concentration in the reaction mixture is 1% v/v. This DMSO concentration has no effect on PDE 3 activity. After the reaction has been started by adding substrate, the samples are incubated at 37°C for 30 minutes. The reaction is stopped by heating the test tubes at 110°C for 2 minutes. The samples remain in ice for a further 10 minutes. Addition of 30 µl of 5'-nucleotidase (1 mg/ml, from a suspension of Crotalus adamanteus snake venom) is followed by incubation at 37°C for 10 minutes. The samples are stopped on ice, 400 µl of a Dowex-water-ethanol (1+1+1) mixture are added to each and, after thorough mixing, they are incubated on ice again for 15 minutes. The reaction vessels are centrifuged at 3000 x g for 20 minutes. 200 µl aliquots of the supernatant are transferred directly into scintillation vessels. After addition of 3 ml of scintillator, the samples are measured in a beta counter. The nonspecific enzyme activities are measured in each case in the presence of 100 µM IBMX in the PDE 3 determination and are subtracted from the assay results.

IC_{50} values for phosphodiesterase 3 inhibition determined for the compounds according to the invention were in the range from 10^{-9} to 10^{-5} M.

For example, the following values were determined for selected examples:

Example	IC_{50} [µmol/l]
1	0.02
5	0.04
7	0.07
8	0.07

Inhibition of phosphodiesterase 5

The PDE 5 activity is determined in enzyme preparations from human platelets. Human blood was anticoagulated with citrate. Centrifugation at 700 × g for 20 minutes at room temperature allows platelet-rich plasma in the supernatant to be separated from the erythrocytes and leukocytes. The platelets are lysed by ultrasound and employed in the PDE 5 assay.

The phosphodiesterase activity is determined by the method described by Thompson et al. (Thompson, W.J.; Appleman, M.M., Assay of cyclic nucleotide phosphodiesterase and resolution of multiple molecular forms of the enzyme. Adv. Cycl. Nucl. Res. 1979, 10, 69-92) with some modifications.

The reaction mixtures contain 50 mM tris-HCl (pH 7.4), 5 mM $MgCl_2$, the inhibitors in variable concentrations, the enzyme preparation and the other components necessary to measure the individual isoenzyme PDE 5 (see below). The reaction is started by adding the substrate 0.5 µm [^{3}H]-cAMP (about 6000 CPM/assay). The final volume is 100 ml.

Test substances are made up as stock solutions in DMSO. The DMSO concentration in the reaction mixture is 1% v/v. This DMSO concentration has no effect on PDE 5 activity. After the reaction has been started by adding substrate, the samples are incubated at 37°C for 30 minutes. The reaction is stopped by heating the test tubes at 110°C for 2 minutes. The samples remain in ice for a further 10 minutes. Addition of 30 µl of 5'-nucleotidase (1 mg/ml, from a suspension of Crotalus adamanteus snake venom) is followed by incubation at 37°C for 10 minutes. The samples are stopped on ice, 400 µl of a Dowex-water-ethanol (1+1+1) mixture are added to each and, after thorough mixing, they are incubated on ice again for 15 minutes. The reaction vessels are centrifuged at 3000 × g for 20 minutes. 200 µl aliquots of the supernatant are transferred directly into scintillation vessels. After addition of

3 ml of scintillator, the samples are measured in a beta counter. The nonspecific enzyme activities are measured in each case in the presence of 100 µM IBMX in the PDE 5 determination and are subtracted from the assay results.

IC_{50} values for phosphodiesterase 5 inhibition determined for the compounds according to the invention were in the range from 10^{-9} to 10^{-5} M. For example, the following values were determined for selected examples:

Example	IC_{50} [µmol/l]
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8	0.07

Induction of NO production in fibroblasts (rat)

Rat fetal lung fibroblasts (RFL-6) represent a suitable medium for investigating the influence of the effect of NO on intracellular cGMP levels (Ishii et al. 1991). The basic mechanism is applicable to smooth vascular muscles.

The compounds according to the invention enhance, in a concentration-dependent manner, the increase in intracellular cGMP levels induced by the NO donor S-nitroso-N-acetyl-D,L-penicillamine.

Thus, compound 1 at a concentration of 0.010 µmol/l for example induces a significant rise in the cGMP level. The activity of compound 1 is thus 10,000 times that achieved by use of the nonspecific PDE inhibitor 3-isobutyl-1-methylxanthine (IBMX).

Circulatory analysis on anaesthetized beagle dogs

4 male beagle dogs with a body weight of 9.0 to 15.0 kg were used for this investigation. The animals were

anaesthetized intravenously with 80 mg/kg cloralose and 400 mg/kg urethane. The dogs were intubated but not artificially ventilated.

The brachial artery was then prepared to record the peripheral blood pressure. A microtip catheter was introduced through the right carotid artery to record the left ventricular systolic/diastolic pressure. The cardiac output was determined by thermodilution. For this purpose, a Swan-Ganz catheter was introduced via the femoral vein. The catheter was positioned so that the blood pressure in the pulmonary artery could be measured at its tip. 3.0 ml of physiological saline (temp. 4.0°C), were injected and the cardiac output was determined from the change in temperature in the aortic trunk.

The surface ECG was recorded from the limbs. The ECG parameters were evaluated automatically.

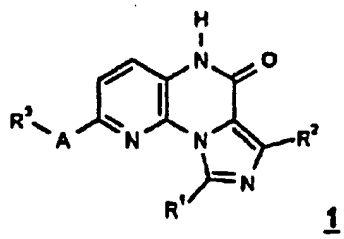
A computer-assisted system acquired and calculated all the blood pressures.

It was possible to show in these investigations that, for example, compound 1 according to the invention after intragastric administration increases the contractility of the heart (increase in the left ventricular rate of pressure rise by up to 4-fold), with an increase of up to two-fold in the cardiac output, in a dose-dependent manner in the dose range from 0.25 to 3.0 mg/kg. Despite the large rise in the cardiac work, there was only a slight initial rise in the arterial blood pressure, and the pressure amplitudes increased. Higher doses reduced the systolic blood pressure slightly.

Despite the huge and long-lasting increase in the cardiac output by compound 1, no hypoxia-related arrhythmias or extrasystoles were observed, which demonstrates the strong coronary dilating action.

Patent Claims

1. Imidazo[1,5-a]pyrido[3,2-e]pyrazinones of the formula 1



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in which

A represents O or NH,

R^1, R^2, R^3 can be identical or different and can denote hydrogen, and

$-C_{1..8}$-alkyl, straight-chain or branched-chain, optionally substituted one or more times by -OH, -SH, $-NH_2$, $-NHC_{1..6}$-alkyl, $-N(C_{1..6}\text{-alkyl})_2$, $-NHC_{6..14}$aryl, $-N(C_{6..14}\text{aryl})_2$, $-N(C_{1..6}\text{alkyl})(C_{6..14}\text{aryl})$, $-NO_2$, -CN, -COOH, $-COOC_{1..5}$alkyl, $-(C=O)C_{1..5}$alkyl, -F, -Cl, -Br, -I, $-O-C_{1..6}$-alkyl, $-O-C_{6..14}$-aryl, $-S-C_{1..6}$-alkyl-$S-C_{6..14}$aryl, $-OSO_2C_{1..6}$alkyl, $-OSO_2C_{6..14}$aryl, mono-, bi- or tricyclic saturated or mono- or polyunsaturated carbocycles with 3..14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles with 5..15 ring members and 1..6 hetero atoms, which are preferably N, O and S,

$-C_{2..8}$-alkenyl, mono- or polyunsaturated, straight-chain or branched-chain, optionally substituted one or more times by -OH, -SH, $-NH_2$, $-NHC_{1..6}$-alkyl, $-N(C_{1..6}\text{-alkyl})_2$, $-NHC_{6..14}$aryl, $-N(C_{6..14}\text{aryl})_2$, $-N(C_{1..6}\text{alkyl})(C_{6..14}\text{aryl})$, $-NO_2$, -CN, -COOH, $-COOC_{1..5}$alkyl, $-(C=O)C_{1..5}$alkyl, -F, -Cl, -Br, -I, $-O-C_{1..6}$-alkyl, $-O-C_{6..14}$-aryl, $-S-C_{1..6}$-alkyl, $-S-C_{6..14}$aryl, $-OSO_2C_{1..6}$alkyl, $-OSO_2C_{6..14}$aryl, mono-, bi or tricyclic saturated or mono- or polyunsaturated carbocycles with 3..14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles with

5..15 ring members and 1..6 hetero atoms, which are preferably N, O and S,

-$C_{2..8}$-alkynyl, mono- or polyunsaturated, straight-chain or branched-chain, optionally substituted one or more times by -OH, -SH, $-NH_2$, $-NHC_{1..6}$-alkyl, $-N(C_{1..6}\text{-alkyl})_2$, $-NHC_{6..14}$aryl, $-N(C_{6..14}\text{aryl})_2$, $-N(C_{1..6}\text{alkyl})(C_{6..14}\text{aryl})$, $-NO_2$, -CN, -COOH, $-COOC_{1..5}$alkyl, $-(C=O)C_{1..5}$alkyl, -F, -Cl, -Br, -I, $-O-C_{1..6}$-alkyl, $-O-C_{6..14}$-aryl, $-S-C_{1..6}$-alkyl, $-S-C_{6..14}$aryl, $-OSO_2C_{1..6}$alkyl, $-OSO_2C_{6..14}$aryl, mono-, bi or tricyclic saturated or mono- or polyunsaturated carbocycles with 3..14 ring members, mono-, bi- or tricyclic saturated or mono- or polyunsaturated heterocycles with 5..15 ring members and 1..6 hetero atoms, which are preferably N, O and S,

-mono-, bi- or tricyclic, saturated or mono- or polyunsaturated carbocycles with 3..14 ring members,

optionally substituted one or more times by -OH, -SH, $-NH_2$, $-NHC_{1..6}$-alkyl, $-N(C_{1..6}\text{-alkyl})_2$, $-NHC_{6..14}$aryl, $-N(C_{6..14}\text{aryl})_2$, $-N(C_{1..6}\text{alkyl})(C_{6..14}\text{aryl})$, $-NO_2$,-CN, -COOH, $-COOC_{1..5}$alkyl, $-(C=O)C_{1..5}$alkyl, -F, -Cl, -Br, -I, $-O-C_{1..6}$-alkyl, $-O-C_{1..14}$-aryl, $-S-C_{1..6}$-alkyl, $-S-C_{6..14}$aryl, $-OSO_2C_{1..6}$alkyl, $-OSO_2C_{6..14}$aryl,

-mono-, bi or tricyclic saturated or mono- or polyunsaturated heterocycles with 5..15 ring members and 1..6 hetero atoms, which are preferably N, O and S,

optionally substituted one or more times by -OH, -SH, $-NH_2$, $-NHC_{1..6}$-alkyl, $-N(C_{1..6}\text{-alkyl})_2$, $-NHC_{6..14}$aryl, $-N(C_{6..14}\text{aryl})_2$, $-N(C_{1..6}\text{alkyl})(C_{6..14}\text{aryl})$, $-NO_2$,-CN, -COOH, $-COOC_{1..5}$alkyl, $-(C=O)C_{1..5}$alkyl, -F, -Cl, -Br, -I, $-O-C_{1..6}$-alkyl, $-O-C_{1..14}$-aryl, $-S-C_{1..6}$-alkyl, $-S-C_{6..14}$aryl, $-OSO_2C_{1..6}$alkyl, $-OSO_2C_{6..14}$aryl.

2. Physiologically tolerated salts of the compounds of formula 1 according to Claim 1, characterized by neutralizing the bases with inorganic or organic acids or by neutralizing the acids with inorganic or organic bases or by quaternizing tertiary amines to give quaternary ammonium salts.

3. Compounds of formula 1 according to Claims 1 and 2 having an asymmetric carbon atom in the D form, the L form and D,L mixtures and, in the case of more than one asymmetric carbon atom, the diastereomeric forms.

4. Compounds of formula 1 according to Claims 1 to 3, in particular one of the following compounds:

8-methoxy-3-methyl-1-propylimidazo[1,5-a]pyrido[3,2-e]-pyrazinone;

8-methoxyimidazo[1,5-a]pyrido[3,2-e]pyrazinone;

8-methoxy-3-methylimidazo[1,5-a]pyrido[3,2-e]-pyrazinone;

8-methoxy-1-methylimidazo[1,5-a]pyrido[3,2-e]-pyrazinone;

8-methoxy-1-propylimidazo[1,5-a]pyrido[3,2-e]-pyrazinone;

1-ethyl-8-hydroxy-3-methylimidazo[1,5-a]pyrido[3,2-e]-pyrazinone;

1-ethyl-8-methoxy-3-methylimidazo[1,5-a]pyrido[3,2-e]-pyrazinone;

1-ethyl-8-(3-hydroxypropyl)-3-methylimidazo[1,5-a]-pyrido[3,2-e]pyrazinone;

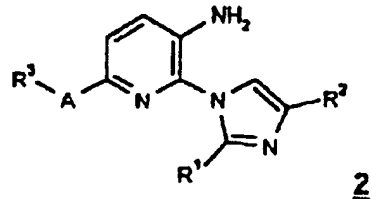
1-ethyl-3-methyl-8-(2-oxopropyl)imidazo[1,5-a]pyrido-[3,2-e]pyrazinone;

1-ethyl-3-methyl-8-(2-pyridylmethyl)imidazo[1,5-a]-pyrido[3,2-e]pyrazinone;

8-methoxy-1-phenylimidazo[1,5-a]pyrido[3,2-e]-pyrazinone;

8-methoxy-3-phenylimidazo[1,5-a]pyrido[3,2-e]-pyrazinone.

5. Process for preparing compounds of formula 1 according to Claims 1 to 4, and of further compounds of formula 1 in which A represents NH, R^1, R^2, R^3 can be identical or different and again have the meaning described in Claim 1, characterized in that 3-aminopyridines of the formula 2 with identical meaning of A, R^1, R^2 and R^3



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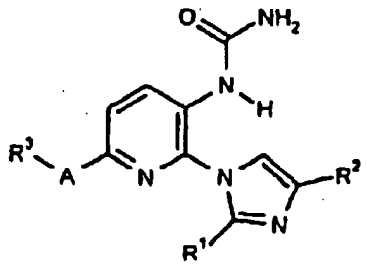
are reacted in an organic solvent in the presence of an acid with a cyanate, and the ureas of the formula 3 with identical meaning of A, R^1, R^2 and R^3 produced thereby



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are subsequently heated in an organic solvent so that cyclization to the compounds according to the invention of the formula 1 takes place.

6. Preparation of compounds of formula 1 by the process according to Claim 5, particularly preferably with use of alkali metal cyanates for obtaining the intermediates of the formula 3.

7. Preparation of compounds of formula 1 by the process according to Claims 5 and 6, particularly preferably with use of protic solvents for obtaining the intermediates of the formula 3.

8. Preparation of compounds of formula 1 by the process according to Claim 5 to 7, particularly preferably obtaining the intermediates of the formula 3 in the presence of a mineral acid.

9. Preparation of compounds of formula 1 by the process according to Claim 8, particularly preferably obtaining the intermediates of the formula 3 in the presence of a concentrated mineral acid which is miscible with the protic solvent used according to Claim 7.

10. Preparation of compounds of formula 1 by the process according to Claims 5 to 9, particularly preferably cyclizing the ureas of formula 3 with use of solvents with a boiling point of > 80°C.

11. Preparation of compounds of formula 1 by the process according to Claim 10, particularly preferably cyclizing the ureas of formula 3, particularly advantageously with use of solvents with a boiling point of > 100°C.

12. Preparation of compounds of formula 1 by the process according to Claims 5 to 11, particularly preferably cyclizing the ureas of formula 3 with use of a reaction temperature of > 80°C.

13. Preparation of compounds of formula 1 by the process according to Claim 12, particularly preferably cyclizing the ureas of formula 3, particularly advantageously with use of a reaction temperature of > 100°C.

14. Use of compounds of formula 1 according to Claims 1 to 4 and of further compounds of formula 1 in which A represents NH, R^1, R^2, R^3 can be identical or different and again have the meaning described in Claim 1, as therapeutic agents for producing medicinal products for treating erectile dysfunction (impotence).

15. Medicinal products containing one or more compounds according to Claims 1 to 4, and further compounds of formula 1 in which A represent NH, R^1, R^2, R^3 can be identical or different and again have the meaning described in Claim 1, in addition to conventional physiologically tolerated carriers and/or diluents or excipients.

16. Process for producing a medicinal product according to Claim 15, characterized in that one or more compounds according to Claims 1 to 4, and further compounds of formula 1 in which A represents NH, R^1, R^2, R^3 can be identical or different and again have the meaning described in Claim 1, are processed, or converted into a form which can be used in therapy, with conventional pharmaceutical carriers and/or diluents or other excipients to give pharmaceutical preparations.

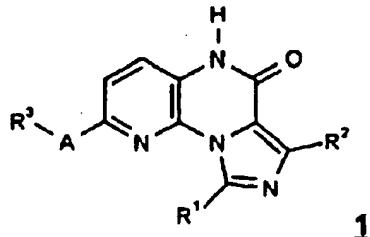
17. Use of compounds of the general formula 1 according to Claims 1 to 4 and of other compounds of formula 1 in which A represents NH, R^1, R^2, R^3 can be identical or different and again have the meanings described in Claim 1, and/or of pharmaceutical preparations according to Claims 15 and 16 alone or in

combination with one another or in combination with carriers and/or diluents or other excipients.

18. Use of compounds according to Claim 1 to 4 and of other compounds of formula 1 in which A represent NH, R^1, R^2, R^3 can be identical or different and again have the meaning described in Claim 1 as therapeutic agents for producing medicinal products for the treatment of erectile dysfunction (impotence) according to Claim 14, particularly preferably by oral, parenteral, buccal or sublingual administration.

19. Use of compounds according to Claims 1 to 4 and of other compounds of formula 1 in which A represent NH, R^1, R^2, R^3 can be identical or different and again have the meaning described in Claim 1, as veterinary medicinal therapeutic agents for the prophylaxis and therapy of erectile dysfunction in male mammals.

20. Use of imidazo[1,5-a]pyrido[3,2-e]pyrazinones of the formula 1



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in which

A represents O or NH,

R^1 and R^2 can be identical or different and can denote hydrogen, and

$-C_{1...5}$-alkyl, straight-chain or branched-chain, optionally substituted one or more times by -OH, -SH, $-NH_2$, $-NO_2$, -CN, -COOH, -F, -Cl, -Br, -I, $-O-C_{1...6}$-alkyl, $-S-C_{1...6}$-alkyl, and

R^3 represents hydrogen, and

$-C_{1...5}$-alkyl, straight-chain or branched-chain, optionally substituted one or more times by -OH,

-SH, $-NH_2$, $-NO_2$, -CN, -COOH, -F, -Cl, -Br, -I, $-O-C_{1...6}$-alkyl, $-S-C_{1...6}$-alkyl or phenyl,

as therapeutic active ingredients for producing pharmaceuticals for treating heart failure, pulmonary hypertension and vascular disorders associated with hypoperfusion.

21. Use of physiologically tolerated salts of compounds of the formula 1 according to Claim 20, characterized by neutralizing the bases with inorganic or organic acids or by neutralizing the acids with inorganic or organic bases, or by quaternizing tertiary amines to give quaternary ammonium salts, as therapeutic active ingredients for producing pharmaceuticals for treating heart failure, pulmonary hypertension and vascular disorders associated with hypoperfusion.

22. In the case of compounds of formula 1 according to Claims 20 and 21 having an asymmetric carbon atom the use of these compounds in the D form, the L form and the, L mixtures and, in the case of compounds of formula 1 according to Claims 20 and 21 with a plurality of asymmetric carbon atoms, the use of the diastereomeric forms and mixtures thereof as therapeutic active ingredients for producing pharmaceuticals for treating heart failure, pulmonary hypertension and vascular disorders associated with hypoperfusion.

23. Of the compounds of formula 1 according to Claims 20 to 22, in particular one of the following compounds:

8-methoxy-3-methyl-1-propylimidazo[1,5-a]pyrido[3,2-e]-pyrazinone

8-methoxyimidazo[1,5-a]pyrido[3,2-e]pyrazinone;

8-methoxy-3-methylimidazo[1,5-a]pyrido[3,2-e]-pyrazinone,

8-methoxy-1-methylimidazo[1,5-a]pyrido[3,2-e]-

pyrazinone;
8-methoxy-1-propylimidazo[1,5-a]pyrido[3,2-e]-pyrazinone;
1-ethyl-8-hydroxy-3-methylimidazo[1,5-a]pyrido[3,2-e]-pyrazinone;
1-ethyl-8-methoxy-3-methylimidazo[1,5-a]pyrido[3,2-e]-pyrazinone;
8-benzylamino-1-ethyl-3-methylimidazo[1,5-a]pyrido-[3,2-e]pyrazinone;
1-ethyl-8-(3-hydroxypropyl)-3-methylimidazo-[1,5-a]pyrido[3,2-e]pyrazinone.

24. Use of compounds of formula 1 according to Claims 20 to 23 as therapeutic active ingredients for producing pharmaceuticals for treating heart failure, pulmonary hypertension and vascular disorders associated with hypoperfusion, characterized in that with these compounds there is dual inhibition - simultaneously and comparably strongly - of phosphodiesterase 3 and phosphodiesterase 5, which achieves a positive inotropic effect on the heart combined with a relief of pressure due to dilatation of arterial vessels by one and the same active ingredient.

25. Pharmaceutical containing one or more compounds according to Claims 20 to 23 in addition to conventional physiologically tolerated carriers and/or diluents or excipients.

26. Process for producing a pharmaceutical according to Claim 25, characterized in that one or more compounds according to Claims 20 to 23 are processed with customary pharmaceutical carriers and/or diluents or other excipients to pharmaceutical preparations and brought to a form which can be used in therapy.

27. Use of compounds of the general formula 1 according to Claims 20 to 23 and/or of pharmaceutical

preparations according to Claims 25 and 26 alone or in combination with one another or in combination with carriers and/or diluents or other excipients.

28. Use of compounds according to Claims 20 to 23 as therapeutic active ingredients for producing pharmaceuticals for treating heart failure, pulmonary hypertension and vascular disorders associated with hypoperfusion, particularly preferably by oral or intravenous, intramuscular, subcutaneous, parenteral, buccal or sublingual administration.